

# ANTIMICROBIAL COMPOSITIONS COMPRISING MINOCYCLINE AND DEGRADATION PRODUCTS OF OXIDIZED CELLULOSE

## FIELD OF THE INVENTION

[0001] The invention relates, inter alia, to the field of pharmaceuticals, and more specifically, but not exclusively, to an antimicrobial composition comprising at least one degradation product of oxidized cellulose (OC) (such as at least one degradation product of oxidized regenerated cellulose (ORC)) and minocycline, methods of preparation thereof and uses thereof.

## BACKGROUND OF THE INVENTION

[0002] Healthcare Associated Infections (HAIs) are infections which occur during treatment for medical or surgical conditions, and may be caused by surgical procedures or devices used in medical procedures, such as catheters or ventilators.

[0003] HAI are becoming a global epidemic, resulting in significant levels of morbidity and mortality, and involving significant health care costs. Health service providers, as well as bodies responsible for payment of associated costs, are focusing on reducing HAIs to improve outcomes and control costs.

[0004] Common types of HAIs include catheter-associated urinary tract infections, surgical site infections, bloodstream infections, pneumonia and *Clostridium difficile* infections.

[0005] Surgical Site Infections (SSI) are a class of HAI which develop following surgery. Types of SSI include superficial incisional SSI, which occurs in the area of the skin where the incision was made; deep incisional SSI, which occurs beneath the incision area in muscle and the tissue surrounding the muscles; and organ or space SSI, which can occur in any area of the body other than skin, muscle and surrounding tissue that was involved in the surgery, including a body organ or a space between organs.

[0006] SSIs are currently treated with systemic antibiotics, requiring high dosage levels, from which only a small percentage of the active substance reaches the target site. However, antimicrobial resistance among the pathogens causing the infection is becoming increasingly problematic, thereby limiting the usefulness of such antibiotics in the treatment or prevention of SSIs.

[0007] Known antibiotic products include Medtronic Antibacterial Envelopes sold under the trademark TYRX™, comprising a combination of minocycline and rifampin, which have been shown to reduce infection associated with medical devices in multiple, randomized, controlled trials; the Codman® Bactiseal® catheter for drainage of external cerebrospinal fluid, which is impregnated with rifampin and clindamycin for reduction of Gram-positive bacteria on surfaces of the catheter tube; Ethicon plus sutures, a range of triclosan-coated sutures including a product sold under the trademark named MONOCRYL® Plus Antibacterial (poliglecaprone 25) Sutures and Plus Antibacterial (polydioxanone) Sutures sold under the trademark named PDS® Sutures; and CollatampG/Septocoll E-Innocoll/Biomet, a gentamicin-soaked Collagen Sponge Dual having a dual principle of action for hemostasis and antibiotic protection.

[0008] Examples of background art include U.S. Publication No. 2014/0031912; In. Surg 2014 (99): 565-570; EP 1263485B1; U.S. Pat. Nos. 9,533,069; 8,646,456; Int. J Biol. Macro. 79 (2015): 76-85; and U.S. Publication No. 2016/0030476.

## SUMMARY OF THE INVENTION

[0009] The invention, in some embodiments thereof, relates to a composition comprising minocycline and at least one degradation product (DP) of an oxidized cellulose, methods of preparation thereof and uses thereof. In some embodiments, the oxidized cellulose is oxidized regenerated cellulose (ORC).

[0010] The present inventors have surprisingly found a synergistic effect between minocycline and at least one degradation product of ORC, such that significantly lower levels of minocycline than are generally known in the art when using minocycline alone can be used to obtain effective antimicrobial activity.

[0011] Specifically, in the composition of the present invention, minocycline may be present at a concentration of from about 0.0126 µg/ml. This is significantly lower than the concentrations in the range of 0.06-0.5 µg minocycline per ml minimum inhibitory concentration (referred to as "MIC") values for *S. aureus* according to CLSI, see Table 1) which are known in the art, thereby resulting in less development of antibiotic resistance and fewer side effects, while providing broad spectrum antibiotic activity.

[0012] The composition, in some embodiments thereof, is suitable for local administration to subjects suffering from or at risk of an SSI, providing a higher level of antimicrobial activity than that of currently known compositions, such that lower amounts of antibiotics than are presently known in the art can be used.

[0013] As used herein, the terms "degradation product of OC" or "degradation products of OC" relate to one or more materials obtained upon degradation of OC, in an aqueous solution such as aqueous biological fluid such as serum, blood, plasma and the like or in non-biological solution such as PBS. As used herein, the terms "degradation product of ORC", or "degradation products of ORC" relate to one or more materials obtained upon degradation of ORC, in an aqueous biological fluid, such as serum, blood, plasma and the like or in non-biological fluid such as a solution of PBS.

[0014] Degradation products of OC (such as degradation products of ORC) may include side products present during the production of OC (such as production of ORC). Degradation products may include products obtained upon further oxidation. Degradants can comprise 2-keton ORC degradants, 3-keton ORC degradants 2,3 dial dolly de cellulose degradants, 2,3-dicarboxyl cellulose degradants, and combinations thereof.

[0015] As used herein, the term "antimicrobial" is intended to include destroying or inhibiting the growth of microorganisms such as pathogenic bacteria.

[0016] The term "antibiotic" as used herein relates to a substance such as a chemical that can destroy harmful bacteria or limit their growth. The substance can be a naturally produced or a synthetic material. In some embodiments, substance can be produced by a microorganism, or can be a semisynthetic substance derived from a microorganism.

[0017] As used herein, the term "minocycline" relates to a long-acting, broad-spectrum, antibiotic drug, C<sub>23</sub>N<sub>27</sub>N<sub>3</sub>O<sub>7</sub>,